REMARKS/ ARGUMENTS

Claims 18-58 are now active in the present application. Claims 21 and 25 have been amended to be independent claims and some additional claims have been added to depend there from. Support for these claims is found in Claims 18-48 and the specification as originally filed. No new matter is added.

Applicants wish to thank Examiners Marvich and Guzo for the courteous discussion granted to the Applicants' undersigned representative on May 13, 2003. During this discussion, the Applicants' representative again clarified that in the Georges publication the HS-TK gene is in the donor T-cell and not the graft recipient T cell as in the present claims. For example, a donor cell and a recipient cell are by their nature going to be genotypically and phenotypically different from each other, e.g., different MHC profiles. In support of this, note that Georges describes selectively killing the donor CTL with gangcylovir, the TK gene is actually transferred into the donor specific cells but not the recipient specific cells as in the present claims (see, for example, the Abstract: "Conclusions"[1] and the discussion on page 542, column 2, paragraph 1[2]). As a result, the claimed product itself is, in fact, different from that in Georges.

In light of the discussion and the comments above, withdrawal of the rejection under 35 U.S.C. § 102(b) over Georges et al is requested.

During the above-noted discussion, the Applicants' representative also explained why the present claims are, in fact, enabled by the specification and the common knowledge in the art and again pointed to publications available at the time of filing for support. A detailed description of those references as well as the references themselves was filed previously.

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1 "We have demonstrated efficient ex vivo transduction, expansion, maintenance of alloreactivity, and gancyclovir-mediated ablation of canine CTL. . ."

2 "This shows that Hs-tk-transduced CTL were specifically killed with ganciclovir, without the emergence of

First it is noted that the rejection under 35 U.S.C. § 112, first paragraph is based on a scope of invention of methods of treating patients by gene therapy and is applied to all of the pending claims. However, only pending claims 44-58 are drawn to such methods. Claims 18-43 are drawn to *in vitro* modified T cells and methods of producing the same.

The Office takes the position that the entirety of the claims are not enabled primarily because of the alleged unpredictability in the art of gene therapy and has cited Marshall et al in support of this position.

The Office has also alleged that the specification does not provide a utility for the use of the claimed modified T cells and as such the claims are not enabled. Applicants respectfully disagree. Applicants respectfully direct the Examiner's attention to MPEP §2164.07(I)(B):

> The Examiner has the initial burden of challenging an asserted utility. Only after the Examiner has provided evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the Applicant to provide rebuttal evidence sufficient to convince one of ordinary skill in the art of the invention's asserted utility. *In re Brana* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (citing *in re Bundy*, 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981)

The specification clearly asserts that one part of the utility of the present invention is to improve upon methods of allogenic graft rejection (page 11 of the application). This is the portion of the utility that the Office has challenged. However, the claimed modified T cells can also be used to study the immunoregulatory potential of T lymphocytes, for example, as it relates to the proliferation inhibition (page 21 of the application), the cells can be used to study the effects of naïve T-lymphocytes, for example to analyze possible modes of action of the modified T cells (page 22), and to study the efficacy of various gene transfer protocols into the modified T graft recipient T cell (pages 22-23 of the application). The Office has not provided any evidence of record to conclude that one of ordinary skill in the art would have

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ganciclovir-resistant T cells."

any basis for doubting these asserted utilities. As a result, there is no doubt that Claims 18-43 are, in fact, enabled by the present application.

The lack of in vivo data for the utility aspect concerning the use for gene therapy, as it relates to other utilities of Claims 18-43 and for the methods in Claims 44-58 indicates the Office may be confusing grounds for patentability with those which the Food and Drug Administration apply in assessing the safety and efficacy of drugs and pharmaceuticals in human patients. First, one must consider now many lives can be saved by knowing that a the *in vitro* modified T cells can be used to treat patients undergoing allogenic grafts.

The Examiner should recognize that before a corporation can contemplate suggesting the use, commercially, of the modified T cells, it is quite likely that Food and Drug approval for the new use would be sought. Obtaining Food and Drug approval is an extremely expensive process. Accordingly, absent the grant of a patent, or some form of exclusivity, an entity would be naturally reluctant to expend the funds necessary to develop the new use invention and obtain FDA approval since there will be no way of recouping the investment.

Accordingly, it is well-established that the basis for patentability is NOT the same basis for obtaining FDA approval because the grant of the patent serves to stimulate research and development and to bring valuable, potentially life saving, products to market. For example, Applicants respectfully direct the Examiner's attention to the Federal Circuit's decision of In re Brana (34 USPQ2d 1436, 1442 (Fed. Cir. 1995)) which states:

> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage of which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require phase 2 testing in order to prove utility, the associated costs would prevent many companies from obtaining a patent protection on a promising new invention, thereby eliminating an incentive to pursue, through research and development, potential cures

in many crucial areas such as the treatment of cancer.

While the disease state at issue in *Brana* was cancer, certainly the Office would agree that transplant therapies are a significant and needed therapeutic to treat a host of devastating diseases. As a result, the possibility that further research and development may be needed to develop actual human clinical protocols does not, and should not, deny the patentability of the present invention.

With respect to the Office's comment that the details for gene therapy are not adequately taught in the specification (page 6 of the Office Action), Applicants point out the following. It is well-established that:

> "'the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.'. A patent need not teach, and preferably omits, what is well known in the art." (MPEP 2164.01, citations omitted).

The relevant threshold is NOT absolute enablement, only reasonably make or use the invention. It is well-known that dosages and treatment regimens are going to vary depending on the nature of the patient's condition, age, sex, nationality, and progression of the disease. These are factors for approval for the use of a drug, pharmaceutical or biologic through the FDA, but are not a basis to deny patentability. There is no question that one of skill in the art can reasonably use the *in vitro* modified T cells particularly in view of the information provided and summarized by Dr. Ritter in the Declaration submitted previously. In particular, Dr. Ritter concluded that, in his opinion the claims are enabled (again pointing out that Dr. Ritter has a Ph.D. in biology with 7.5 years as a scientist). Dr. Ritter has pointed to a number of scientific publications as a basis for concluding that the expectation of successfully

using the modified T cells for human therapy is reasonable.

In view of the above, Applicants request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

The rejection of Claims 21, 23-27 and 25-41 under 35 U.S.C. § 112, second paragraph is addressed by amendment. Withdrawal of this ground of rejection is requested.

The objections noted for Claims 35, 37, 38, 39, 40 and 41 have been addressed by amendment

In the event the Examiner's requires clarification on any issue in this case, she is invited to contact the Applicants' undersigned representative to resolve the matter expediently.

Applicants also request that this application be passed onto issuance.

Respectfully submitted,

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